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The alleged association between artificial fluoridation of water supplies and cancer: a review

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Since 1945, artificial fluoridation of water supplies has been used with success to reduce the incidence of dental caries in many areas where the natural fluoride content of the water is low. However, since 1975, it has been maintained that such artificial fluoridation is followed by an increased risk of cancer. These allegations originate from a single source. The present review, which covers re-examinations of the same data as well as evidence from scientific and governmental bodies in many countries, shows these assertions to be erroneous.

EARLY HISTORY OF FLUORIDATION

A preventive effect against dental caries, from fluoride in drinking-water, was first suggested in 1933 by Ainsworth, who in a study of the dental health of residents in Maldon, England, associated the prevalence of dental mottling in that town with its water supply, which contained up to 5.5 mg/l (5.5 ppm)[a] of fluoride (*1*). Despite the frequency of dental mottling, the prevalence of dental caries in the permanent teeth of schoolchildren in this community was 7.9%, compared with 13.1% in children of similar age residing in other towns of England and Wales. In 1937, Klein & Palmer reported from the United States that the lowest caries attack rates occurred in endemic fluorosis areas (*20*). They suggested that fluoride in the water provided the explanation for this observation.

Artificial fluoridation of drinking-water seems to have been first introduced in January 1945 in Grand Rapids, Michigan, in the USA. It was soon widely adopted, and the American Dental Association, in a hearing before a Committee of the House of Representatives, reported that on 14 May 1954 a total of 16 847 209 persons in 994 communities in 43 States and Panama, Puerto Rico and Washington, DC, were drinking water with controlled amounts of fluoride added (*31*).

Until 1954, the fluoridation of water supplies seems to have been unopposed, but in that year a bill was presented to the United States Congress to prevent the procedure, motivated largely, it seems, by general juridical and toxicological considerations, as well as some doubts about the preventive action on dental caries. The bill, however, failed to be adopted.

Early comparative studies using mortality data

In the USA. Studies in the United States, using specific mortality data from communities with either virtually fluoride-free or fluoride-bearing water supplies, failed to show a significant difference in mortality between cities belonging to these two categories. Thus, Hagan et al. from the Division of Dental Public Health, Bureau of State Services, US Public Health Service, in 1954 compared the mortality data from 32 pairs of cities where the majority of the analyses of their water supplies indicated either the presence of fluoride in concentrations ≥ 0.70 mg/l (high fluoride), or ≤ 0.25 mg/l (low fluoride) (*13*). The study included cities with a population of 10 000

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[a] To conform with SI usage, ppm (parts per million) in this review is expressed as mg/litre; the numerical part always remains the same, e.g., 0.2 ppm = 0.2 mg/l.

or more, according to the 1950 census, and involved a total population of 892 625 persons in cities belonging to the high-fluoride group and 1 297 500 in cities from the low-fluoride group. The 32 pairs of mortality rates from all causes and rates for specific disease mortality were brought together. The average mortality rate from all causes of death was 1005.0 per 100 000 population in the low-fluoride cities and 1010.6 in the high-fluoride cities. In the individual pairs, a higher mortality rate was observed in equal numbers of high- and low-fluoride cities.

There was no statistically significant difference between the two groups of cities in the mortality rates from all causes of death or from heart disease, cancer, intracranial lesions, nephritis, or cirrhosis of the liver. Cancer deaths occurred at the average rate of 139.1 per 100 000 population in the low-fluoride cities and 135.4 per 100 000 in the high-fluoride cities. In half of the 32 pairs, the rates were lower in the high-fluoride cities.

In England. In 1962, the possible harmful effects from fluoridation of drinking-water were examined in a detailed study in England by Heasman & Martin from the Ministry of Health, London (*14*). They compared the mortality rates from various diseases (including all cancers, cancer of the stomach and of the lung, and leukaemias) for 18 urban areas (in the south and north) that had a high fluoride content in drinking-water, with paired control areas that had a low fluoride content. In the southern group, it was found that stomach and lung cancers and leukaemia were among the diseases without significant differences in the mortality rates between the high-fluoride towns and their controls. The standardized mortality ratios (SMRs) for all cancers, except cancers of the stomach and lung and leukaemia, were significantly higher in the control (low fluoride) areas. The SMRs for "all other diseases" showed a significant excess in the high-fluoride areas, though they were, as in the case of certain non-malignant diseases, below the national average. In the north, the findings were less clear owing to difficulties in finding adequate control areas.

Other considerations. It follows from the limited information now available on the duration of cancer induction periods in man (the so-called latent period) and their dependence on exposure intensity that, unless it were a case of tumour promotion, an increase in mortality, e.g., from gastric cancer, due to the fluoridation of drinking-water could not be expected to be demonstrable before at least 15 years had passed. For this reason, it was particularly appropriate that the early studies compared areas with different natural fluoride contents in drinking-water. It may still be a matter for speculation whether, as pointed out by Heasman & Martin, the content of 1 mg/l of fluoride in tea may confuse the issue, in places where a considerable amount of tea is drunk. Theoretically, it would therefore have been desirable if some of the studies had been accompanied by statements on the incidence of dental caries within the areas in question.

It is well known that the increase in morbidity associated with malignant neoplasms as an entity, at least in developed countries, is to a considerable extent due to the increase in bronchial carcinoma, particularly among men. Equally interesting to note in the present context is the fact that morbidity from gastric cancer has been decreasing in both males and females, as shown by reliable statistics both from the United States (*9*) and from western Europe (*8*), although the reason for this development is obscure.

IS THERE A CASE AGAINST FLUORIDATION?

The allegations of Yiamouyiannis & Burk

Allegations of an association between artificial fluoridation and cancer were first presented in 1975 by Dr John A. Yiamouyiannis and Dr Dean Burk. A report by these authors of a comparison of crude (all ages) cancer mortality rates for 10 fluoridated and 10 nonfluoridated cities in the USA was cited in the Congressional Record (*3*) of the United States House of Representatives, but as this study attracted considerable criticism, mainly because of its use of crude rates, a revised study was published by the same authors in 1977 (*30*). Since Yiamouyiannis, in his evidence before a Congressional Subcommittee (House of Representatives, 95th Congress, First Session, 21 September to 12 October 1977), referred only to this later paper, this review will concentrate on that version.

This later version has also been criticized statistically in many ways, mostly because of the failure of the authors to consider some essential characteristics of cancer, e.g., the multitude of malignant neoplasms of various types caused by different carcinogens, of which those known so far produce only a few types each in man. Since malignant neoplasms usually develop after exposure to carcinogens for many years, mostly for decades, the morbidity rates will increase steeply in the older age groups. In a number of developed countries, more than half the cancer cases occur after the age of 65, the frequency depending on socioeconomic conditions and ethnic factors of undetermined nature.

In their 1977 publication (*30*), Yiamouyiannis & Burk described the 10 largest, fluoridated, centrally

situated cities in the United States as the study group. In 1953, the year closest to the time of initiation of fluoridation for which cancer death rates are available from the National Center for Health Statistics, the cancer death rate for each of these cities was above 155 per 100 000 inhabitants. The 10 largest centrally situated cities in the United States not fluoridated as of 1969, but with a 1953 cancer death rate greater than 155 per 100 000 per year, were taken as the control group; it may be noted that Boston, Cincinnati, and New Orleans were included in this group. The annual cancer deaths from 1952 to 1969 among residents of these cities (study group and controls) were obtained from the local authorities for age groups 0–24, 25–44, 45–64 and over 65 years, together with data on race and sex.

To study the effects of artificial fluoridation, calculations of the total cancer death rate were made, year by year, for the periods prior to fluoridation in the study group (i.e., 1940 to 1950) and after fluoridation in this group but before any fluoridation in the control group (i.e., 1953 to 1969). In addition, linear regression analysis was carried out on cancer death rates from 1952 to 1969 for each of the age groups 0–24, 25–44, 45–64 and over 65 years. All the averages of cancer death rates were unweighted. Age-adjusted cancer death rates were also computed by the direct method, using a reference population with an age distribution intermediate between the control and study groups. The crude cancer death rates of both groups of cities had a strikingly similar trend between 1940 and 1950. Subsequent to fluoridation, however, an equally striking divergence could be observed which was maintained till 1969, the last year of the study. An increase in crude cancer death rates could be observed in virtually all of the fluoridated cities when compared with the control cities, indicating that the difference in averages was not due to a sharp increase in cancer death rate of only one or two of the fluoridated cities.

Aware of the possible significance of differences in distribution by race or age, Yiamouyiannis & Burk made various attempts to compare the study and control groups in these respects. However, their attempts have been criticized for being based on age groups that were too broad, for being carried out on one factor at a time, and because their suggestion that the US Standard Population may not be representative of the racial composition of the cities they studied was made without supporting evidence.

Refutation of Yiamouyiannis' & Burk's conclusions

Detailed testing of Yiamouyiannis' & Burk's hypothesis was performed by the staff of the National Cancer Institute (NCI) of the USA, on behalf of which D. S. Frederickson, in a letter to the Hon. J. D. Delaney dated 6 February 1976 (*11*), noted that in the period 1950–70 the proportions of the non-white population and of the white population over the age of 65 both rose faster in the 10 fluoridated cities than in the 10 nonfluoridated cities. Since it is known that non-whites have a higher risk of cancer than whites, and that older persons are at greater risk than younger persons, it is standard biometric practice to apply appropriate corrections for such changes in the character of the populations before a valid comparison of trends can be drawn.

The staff of the Epidemiology Branch, National Cancer Institute, computed the number of cancer deaths that would normally be expected in populations resembling those in the two groups of cities under study, using statistics on the age-, race-, and sex-specific mortality rates for all malignant neoplasms in the total population of the United States. These rates were applied to the two groups of cities in 1950, 1955, 1960 and 1970. The numbers of deaths reported from the two groups of cities were then divided by the expected numbers and expressed as quotients designated as SMRs and plotted for the period 1950 to 1970. The results showed very little difference in the trend curves of the two groups of cities. Specifically, the ten fluoridated cities had an SMR of 1.23 in 1950 prior to fluoridation and of 1.24 in 1970. The nonfluoridated group showed an SMR of 1.15 in 1950 and 1.19 in 1970.

It appeared therefore that the differences in the trend of crude cancer mortality rates between the two groups of cities could be attributed to differences in the racial and age composition of the populations involved. In a paper published in 1977 (*23*), Oldham & Newell (see below) came to the same conclusions as Frederickson and his staff.

In a hearing before the relevant subcommittee in the House of Representatives on 21 September 1977, Yiamouyiannis commented on Frederickson's letter (*32*).

1. He found that the number of cancer deaths in nonfluoridated cities, as stated by the NCI, had been seriously in error by reporting 14 487 deaths when the correct value was 14 272. In reply, Dr G. R. Newell explained the difference as being due to the inclusion of the number of deaths for Suffolk County, Massachusetts, with the denominator from the metropolitan area of Boston. However, this error represented only a minute difference in the end result, making an increase of 2% instead of 3% for the nonfluoridated cities.

2. He objected that NCI had disregarded most of the data available on cancer deaths from 1950 to 1969, and had used data from 1970, when fluoridation of the control group had already begun. To this, Dr Hoover pointed out that 1970 had been used because

it was 20 years after the start of fluoridation and it was also a census year. He further pointed out that the removal of Seattle and Atlanta, which had been fluoridated in 1969, would still result in a rise of about 2% for the nonfluoridated cities between 1950 and 1970.

3. Finally, Dr Yiamouyiannis claimed that the NCI had made false assumptions, that the national cancer mortality figures reflected the cancer death rate distribution according to age, race, and sex occurring in the central cities, and that the age, race and sex distribution remained constant for the entire 20 years of the study.

Other objections

Strassburg & Greenland (*27*), from the Los Angeles Department of Health Services and the University of California at Los Angeles, in a clear analysis pointed to a number of fallacies in an early paper by Yiamouyiannis, which was published in 1975 (*29*) and which, they claimed, had an influence on the defeat of a fluoridation proposal in the Los Angeles area.

First, Strassburg & Greenland pointed out that the three nonfluoridated cities — Boston, Cincinnati and New Orleans — with, respectively, 20%, 26% and 27% higher cancer death rates than the national average, had been excluded from Yiamouyiannis' study on the grounds that they were "aberrant" cities, their higher cancer rates having been linked previously to other water-borne contaminants, such as chlorine, chlorinated hydrocarbons, pesticides and herbicides. However, in the subsequent publication (*30*) by Yiamouyiannis & Burk, in 1977, the three cities mentioned were included.

Second, it was pointed out by Strassburg & Greenland that the fluoridated cities had the highest cancer death rates in 1950, as well as in 1970, and that the rate of increase in the nonfluoridated cities during this period was exactly the same (15%) as in the fluoridated cities.

Thirdly, the authors demonstrated that the level of industrialization, as measured by the percentages of the work force employed in manufacturing industries, was much higher for the fluoridated cities than for the nonfluoridated, and pointed out that a higher level is usually accompanied by a higher incidence of cancer.

The National Cancer Institute's study

A report from the National Cancer Institute was published by Hoover et al. in 1976 (*15*) and included studies of the following:

(1) Areas with very high, intermediate, and low (near zero) levels of natural fluoridation.

(2) Changes in cancer mortality by 5-year periods before, during, and after fluoridation.

(3) Time trends, by specific cancer sites, controlling for known cancer-related demographic variables and contrasting these trends with the situation in which only the presence or absence of fluoride was considered.

(4) Changes in cancer morbidity rates for two contrasting cities, one nonfluoridated and the other fluoridated by 1955.

The natural fluoridation study was conducted in Texas and compared counties according to the following levels of fluoridation: intermediate, 0.7–1.2 mg/litre; high, 1.3–1.9 mg/litre; very high, $\geqslant$ 2.0 mg/litre. The demographic, social and economic characteristics of the counties were ascertained and data provided on the numbers of cancer deaths according to age, race, and sex. Age-standardized death rates from cancers at 35 sites were calculated for white males and females for the period 1950–69, for 5-year age groups up to age 74, as well as for the age groups 75–84 and $\geqslant$ 85 years. The analyses were limited to whites because the population estimates for this group were more reliable. The counties were further classified according to the level of urbanization and socioeconomic categories, and SMRs were used for comparisons.

If natural fluoridation did affect the cancer risk, a steady increase in the SMRs with increasing level of fluoride would be expected; however, the SMRs for all sites combined were remarkably uniform (1.0) for each fluoride level up to the highest, where the SMR fell to 0.9 for both sexes.

To get better controls for urbanization, socioeconomic class, and other relevant variables, weighted multiple regression analyses were first carried out. It was also attempted to explain the sex- and site-specific cancer mortality by considering certain socioeconomic and ethnic variables. Second, the weighted average fluoride concentration for each county was included as a possible "explanatory" model, and its effect tested for statistical significance. In the case of SMRs for all cancers, the fluoride variable was negatively related to the age-adjusted mortality rate, but this negative association did not approach statistical significance.

In four analyses of mortality from rectal cancer in males, ovarian cancer in females, and brain cancer in both sexes, higher fluoride concentrations were significantly related to *lower* mortality rates. However, in 64 independent tests of significance, it might be expected that 3 could occur by chance alone at the 0.05 level. The authors suggested that the association with brain cancer might be worth investigating further since it occurred for both sexes and was consistent with the SMR analysis (SMR 0.7 for the high-

est level of fluoride).

Artificial fluoridation was studied in counties where communities comprising at least two-thirds of the total county population (according to the 1960 census) had first been fluoridated in one of three time-intervals (1950–54, 1955–59, or 1960–64). The control counties were those in which no communities had fluoridated their water supply before 1970. Counties with communities having naturally fluoridated water systems were not eliminated from either the exposed or control groups, since the natural fluoridation study had shown essentially no effect of natural fluoridation on cancer risk. Because this analysis was based on time trends, age-adjusted rates were calculated for the 5-year intervals 1950–54, 1955–59, 1960–64, and 1965–69 for each grouping of counties. The relationship measured was the ratio of age-adjusted rates in the several groupings of fluoridated counties to those in the control counties. Summary SMRs were calculated for the 5-year intervals before, during, and after fluoridation in a way similar to the method used in the natural fluoridation study.

Regression analysis similar to that used in the natural fluoridation study was also used for re-analysis of the report by Yiamouyiannis & Burk. Since this analysis involved large urban areas throughout the United States, the percentage of employed persons engaged in manufacturing industries and the geographical region of the country were introduced as variables. If fluoridation caused an increased cancer risk in the way asserted by Yiamouyiannis & Burk, then the ratio of age-adjusted cancer deaths in fluoridated and in nonfluoridated counties should increase with time after fluoridation. This trend was not seen for either men or women. The rates for both men and women in the counties fluoridated in 1950–54 were found to be 10% greater than those in the nonfluoridated counties in 1950–54 and in each successive 5-year interval. The results for counties fluoridated in 1955–59 and 1960–64 were similar and established the consistency of the ratios 5 and 10 years before fluoridation. It is important to note that for counties fluoridated after 1954, i.e., counties for which pre-fluoridation and post-fluoridation data were available, the cancer death rates before fluoridation were higher than those in the control counties.

The SMRs for the 5-year periods showed no important variations in the risks over time, but presented a striking uniformity; this applied to the results from analyses of data both for the sites chosen because of a prior suspicion of an effect and for those where no such suspicion existed. Furthermore, use was made of the morbidity data of the Second and Third National Cancer Surveys for 1947–48 and 1969–71, respectively. From the areas covered by the surveys, the authors selected Birmingham, Alabama, as being largely unfluoridated and Denver, Colorado, as the fluoridated area most likely to uncover an effect of fluoridation on cancer risk. However, the ratios moved in the same direction for both sexes for only 2 out of the 22 tumours compared. The relative risks in the Third Survey fell well within the confidence limits of the Second, indicating no statistically significant difference. Thus, no significant excess mortality from cancer could be detected up to 15 years after fluoridation in areas where 95% of the population were abruptly, and then continuously, exposed to fluoride.

The possibility that a latent period longer than 15 years might be involved was then evaluated in a study of communities that had long been exposed to natural fluoride at various levels. In accordance with findings from the United Kingdom by Kinlen (*16*) and by Nixon & Carpenter (*22*), the cancer risk was not found to be elevated in such areas. So, after application of the methods described to 35 sites of malignant neoplasms in the two sexes for various 5-year periods related to fluoridation, Hoover et al. (*15*) found no support for the claim that fluoridation of water supplies in the United States had increased the risk of cancer.

The data analysed by Oldham & Newell

On approaches made by the Royal College of Physicians of London, the Royal Statistics Society in 1977 commissioned a report on the subject of water fluoridation and cancer by P. Oldham & D. Newell (*23*). Analysing the basic data of Yiamouyiannis & Burk, these authors found that the cities that were later fluoridated had in 1950 reached a 33.8 per 100 000 (23%) excess cancer mortality above the rate of 146.9 per 100 000, as expected from the National Census population for that year. The cities not fluoridated had a 23.5 per 100 000 (15%) excess cancer mortality above their expected rate of 155.5 per 100 000. Thus, though their crude cancer mortality rates in 1950 were similar (180.8 and 179.0), both groups had an excess over expectations and the cities that adopted fluoridation later on were more affected by the excess factor to the extent of 10.3 per 100 000.

From census data for the United States for 1950 and 1970, and the US national age-, sex-, and race-specific mortality rates for all forms of cancer, the pattern of these rates appeared extremely complicated. Up to age 15, and above age 75, the ranking (in order of increasing magnitude) was non-white female, non-white male, white female, and white male. For the age groups $\geqslant 25$, $\geqslant 35$ and $\geqslant 45$ years, the non-white female rate was the highest; for the age group $\geqslant 65$ years, it was again the lowest. The white female rate showed a similar but less violent swing. Both sexes for non-whites show a sudden change in

the sequence of rates for the age groups ⩾ 55, ⩾ 65 and ⩾ 75 years.

Analysis showed that the discrepancy of 8.6 per 100 000 (155.5 minus 146.9), already alluded to, was mostly produced by the excess in nonfluoridated cities of elderly white women and the smaller excess of elderly white males. These excesses were not counterbalanced by the deficiency of non-white persons at younger ages.

In 1950, then, the cities that were later fluoridated had a 10.3 per 100 000 larger excess cancer mortality than the nonfluoridated cities, which, offset by their 8.6 per 100 000 smaller expected mortality, generated crude death rates that made the two sets appear falsely similar.

On the assumption that the unknown causes of the initial excess cancer mortality in the cities that later adopted fluoridation, over those that did not, remained of equal force during the next 20 years, and using the same national death rates, Oldham & Newell repeated the calculations on the populations in 1970 of the two groups of cities. They found that the expected numbers of deaths gave rates of 174.74 and 165.99 for fluoridated and nonfluoridated cities respectively, while the observed numbers gave rates of 217.38 and 197.16 (all figures per 100 000). Thus, in 1970 the fluoridated cities had a 42.64 per 100 000 excess cancer rate (24%) above their expected 174.74, while the nonfluoridated cities had a 31.17 per 100 000 excess cancer rate (19%) above their expected 165.99.

In absolute terms, the excess cancer rate increased between 1950 and 1970 by 8.8 per 100 000 in the fluoridated cities and by 7.7 per 100 000 in the nonfluoridated, a difference of 1.1 per 100 000 to the disadvantage of the fluoridated cities. In proportional terms, the excess cancer rate increased by 1% in the fluoridated cities and 4% in the nonfluoridated, a difference of 3% to the disadvantage of the nonfluoridated cities. Traditionally, epidemiologists would report such differences in proportional terms, which in this case shows a small advantage in fluoridation. However, Oldham & Newell deliberately reported the difference in absolute terms also, showing a small disadvantage in fluoridation, in order to demonstrate the small size of the difference and the fact that the conclusion depends on the type of analysis used.

After commenting on the straightforward but misleading use of crude mortality rates for subsequent years between 1950 and 1970, Oldham & Newell considered a typescript submitted to them by Burk, Yiamouyiannis, Cook & Stern, entitled "Fluoridation-linked human cancer mortality". Since this text includes analyses separately for age groups 0-24, 25-44, 45-64 and ⩾ 65 years, Oldham & Newell warn about very large differences found by themselves in the three age groups, 65-74, 75-84 and ⩾ 85 years, between the sexes and between age groups. In these age groups, which include nearly half the total number of cancers, they had also found considerable differences between the fluoridated and nonfluoridated cities among white males and females but not among non-whites. They summed up the problem by saying that any analysis which puts together all persons over 65 years regardless of race, or all the non-whites regardless of age, would obscure rather than clarify any real difference.

Oldham & Newell finally commented on the criticism by Burk (in a statement to a United States House of Representatives Subcommittee in June 1976) (*4*) of the analysis by Hoover et al. for the National Cancer Institute (*15*). They pointed out that it was a misunderstanding to believe that Hoover et al. had used only one age group for their comparison. The data had led to the same SMRs as those emerging from Oldham's & Newell's own calculations. To the criticism of the use of SMR, they pointed to the advantages in this commonly used procedure. Since they found very little difference between the changes in SMR over the 20-year period studied in the fluoridated and nonfluoridated areas, it follows that *if* a positive association is found between fluoridation and cancer mortality in some age-sex-race groups, then a counterbalancing *negative* association will be found in other groups.

No abstract could possibly do full justice to the clear presentation by Oldham & Newell of the apparently striking observation which originally faced Burk & Yiamouyiannis, and of the inadequacy of the latter's method for its analysis.

The data analysed by Taves

Taves, from the University of Rochester, New York, quoted the data originally presented by Burk & Yiamouyiannis in 1975 on 9 specific cancer sites (7 for white males and 2 for white females) (*28*). Taves reported that the fluoridated cities showed 25 more cancer deaths per 100 000 population than the nonfluoridated cities. He also observed that the fluoridated cities were predominantly in the east and the nonfluoridated mostly in the west of the USA, and that the fluoridated cities showed higher cancer mortality rates than the nonfluoridated controls.

The data, suggesting a change in cancer rates with time, had been submitted to the National Cancer Institute by Yiamouyiannis & Burk in September 1975, and Taves presented a revised version of these data, giving the running average annual crude mortality rates for the 10 fluoridated cities and 6 of the listed nonfluoridated cities, plus 4 other control cities. The latter were selected from the next 5 largest nonfluoridated cities that had average crude death rates, prior to 1952, that were the same as those for the fluoridated cities. It appeared that the average crude

mortality rates diverged markedly subsequent to 1952, the time when these cities initiated fluoridation. Taves observed that it may have seemed unlikely that changes in population characteristics could explain the divergence, but it seems equally unlikely that the effect of fluoridation would be seen in cancer mortality rates almost instantly.

Quoting from the report by Hoover et al. (*15*), Taves presented regression analyses for each of the 9 cancer sites and for the counties of the cities in question, using fluoridation as an independent variable alone and then after correction for demographic variables. When only the fluoridation status of the cities was considered, the slopes of the regression lines were generally positive, and the F values (associated with the fluoride variable) were generally larger than 6, thus supporting Yiamouyiannis' contention that cancer of some sites showed a higher mortality in the fluoridated counties.

However, when the 6 demographic risk factors are taken into account, the F values become insignificant, except in the case of cancer of the stomach. According to Hoover et al. (*15*), further regression analysis allowing for control of the ethnic groups at high risk for stomach cancer yields a non-significant F value of 0.02 for females and a value of 6.9 for males ($P < 0.05$). Since one "positive" site could be due to chance, this does not prove that fluoridation and cancer of the stomach are linked, but the finding cannot be ignored since fluoride could be expected to be present as hydrofluoric acid in the stomach. Nevertheless, this suspicion was not borne out when the 20-year period was broken down into 5-year periods in order to see the changes with time for all the US counties in which at least two-thirds of the population had first been exposed to fluoridation in one of the first three 5-year periods. Neither for stomach, nor for bone and kidney, in which organs fluoride is concentrated, was there any suggestion of an increase in cancer mortality rates; in fact there was possibly a decrease.

The assertion that divergence in the crude mortality rates was due to fluoridation was, in Taves' opinion, clearly refuted only when Frederickson, from the US National Cancer Institute, in 1976 reported standardized mortality ratios for the cities in question (*11*). These were determined by dividing the observed yearly mortality by the expected mortality, based on the number of people in each age group for each sex and race (white, non-white) multiplied by a single, standard total cancer rate for each of the categories, as observed for the population in the USA as a whole in 1950.

The results confirm that the fluoridated cities had higher mortality rates than the controls, but there was no suggestion of a change with the introduction of fluoridation. In an attempt to gain more precision, Taves averaged the cancer mortality observed in the year prior to the census year with the figures for the census year. He noted, in analysing these data, that only one of the fluoridated cities had gained in population from 1950 to 1970, whereas 7 of the 10 non-fluoridated cities had gained in population. Therefore, the 10 next largest fluoridated cities were also considered, and it appeared that 7 of them showed an increase in population and so were more comparable to the controls.

The SMRs for the second set of fluoridated cities were considerably lower than those for the control cities, and were remarkably constant over the 20-year period, showing no difference in relation to the non-fluoridated cities. The rates in the fluoridated cities were higher only for a particular set of fluoridated cities, and the higher rates in these cities were present even prior to fluoridation. Numerical considerations based on the available evidence cannot, in Taves' opinion, rule out the possibility of fluoridation causing a 1.5% increase in total cancer rates or a 15% increase in specific cancer rates. In summary, however, he found that the available evidence did not suggest that fluoridation had increased or decreased the cancer mortality rates, and the margin of error was as low as 3 per 100 000.

The data analysed by Kinlen & Doll

Kinlen & Doll (*17*) from Oxford, England, in 1977, also took issue with the statement by Burk & Yiamouyiannis concerning increasing trends in cancer mortality in the fluoridated American cities.

Kinlen & Doll examined the demographic data for the 20 cities that had been used in the discussions following the publication by Burk & Yiamouyiannis, and found that the proportion of the non-white population and the proportion over 65 years of age had increased more rapidly in the fluoridated than in the nonfluoridated cities. Since cancer incidence increases rapidly with age, these authors standardized the rates by the usual indirect method using, as a standard, the specific national cancer mortality rates for the United States for the corresponding years for each sex, ethnic and 10-year age group. The ratio of the observed to the expected numbers of deaths from cancer fell slightly in the fluoridated cities and did not change in the nonfluoridated cities. Kinlen & Doll refuted the suggestion that there were extreme or irregular changes in the age structure of the populations in the fluoridated and nonfluoridated cities listed in their tables and found no reason to suppose that fluoridation was associated with an increase in cancer mortality, let alone caused it.

In 1981, the same authors re-examined the United States data, this time using a direct method of standardization, and compared the results with those

obtained by the indirect method (*18*). They found that the relative excess mortality from cancer had not increased since 1950, if allowance was made for changes in the sex, age and ethnic group constitution of the population by any of the standard methods. On the contrary, it had decreased slightly, no matter which of the appropriate methods of comparison was chosen.

ASSESSMENT OF CANCER MORBIDITY AND MORTALITY DATA IN SEVERAL COUNTRIES

As a result of the increasing efficacy of modern therapy, cancer mortality rates are becoming increasingly inadequate as a measure of the true incidence or morbidity of the disease. This is now determined by cancer registration in many places all over the world. Since such systems have access to mortality data as well, their coverage will be more complete than the use of mortality data alone, which may not have the advantage of histological diagnoses. During recent decades, cancer registration has therefore become an indispensable tool in the analysis of carcinogenesis in man (*8*).

Australia

Richards & Ford (*25*), from the Central Cancer Registry of New South Wales, in 1979 examined the cancer mortality rates in selected localities with fluoridated and nonfluoridated water supplies, in New South Wales. Age adjustment was made by indirect standardization. Several places in New South Wales with a high naturally occurring fluoride content in their water supplies had to be excluded because of lack of suitable data. Localities with a fluoridated water supply were included only if their fluoridation schemes had been operating for five years or more.

The number of deaths ascribed to malignant neoplasms in 1970–72 in each 5-year age group was obtained for New South Wales from the Australian Bureau of Statistics. Using the annual average number of deaths and the census population of 1971, the standardized mortality ratios were calculated and applied to the populations of the selected localities. The number of deaths observed in these localities as annual averages for 1970–72 were also obtained from the Australian Bureau of Statistics, and the observed/expected ratio was determined, and multiplied by 100 to obtain the SMR.

The SMRs for both fluoridated and nonfluoridated localities were found to cover a wide range. Yass, with the earliest recorded fluoridation scheme in New South Wales, had a lower SMR than Gosford (nonfluoridated); in 1970–72, Gosford (nonfluoridated) had a higher SMR than Wyong (fluoridated) and both shires had SMRs close to the average for New South Wales. Two of the selected localities, Queanbeyan (fluoridated) and Lismore (nonfluoridated), had SMRs significantly lower than the New South Wales average ratio ($P < 0.05$).

It appeared from the aggregated data that the SMR for the 10 localities with fluoridated water supplies (91.6) was slightly lower than the SMR for the 10 that were nonfluoridated (94.9). It was concluded that in New South Wales the differences in cancer mortality, expressed as SMRs, are unrelated to whether a locality has a fluoridated water supply or not.

Austria

In 1977, Binder (*2*) from the Vienna Health Service compared cancer mortalities in Austrian villages with a fluoride content of more than 1 mg/l in drinking water with data from villages with a fluoride level of below 0.2 mg/l. A total of 5005 deaths were studied, all from the period 1955–74, with the exception of a single village whose water supply history made 1951–70 more relevant. Care was taken to exclude persons who had not spent their whole life in the village in question.

The percentage of deaths from cancers in various sites in relation to all deaths (after exclusion of perinatal and accidental deaths) was classified into 10-year age groups and by province; all of them were higher in the areas with a low fluoride content.

Canada

The first municipalities in Canada to introduce fluoridation were Brantford and Sudbury (both in Ontario) in 1945 and 1952 respectively. During the following two decades a large number of municipalities introduced this practice, so that in 1977 a population of about 8.6 million was supplied with water in which the level of fluoride was adjusted to the optimum level for good oral health.

In a report from the Canadian National Health and Welfare Department in 1977, Raman et al. (*24*) studied 79 groups of municipalities throughout Canada to determine if fluoridation of water supplies increased the risk of death from cancer for residents. The study period covered 1954–73 inclusive, and death rates from cancer were compared between groups of fluoridated and nonfluoridated municipalities.

In addition to mortalities from all neoplasms and all malignant neoplasms, those relating to the following were also of interest: all forms of leukaemia and malignant neoplasms of the respiratory system, small and large intestines, rectum and rectosigmoid junction, and stomach. Comparisons were made, within groups of municipalities that had fluoridated at about

the same time, of the death rates from all neoplasms and all malignant neoplasms.

No appreciable differences in death rates from all types of cancer or from any specific tumour site were noted between fluoridated and nonfluoridated municipalities over this period. Nor were any significant differences apparent within the same group of municipalities between death rates from all types of cancer prior to and after fluoridation.

The authors recognized that, since most municipalities in Canada had received fluoridated water for 20 years or less, the period covered by their study was shorter than the latent periods for cancer development associated with some carcinogens in man. However, it was pointed out that the conclusions of Yiamouyiannis & Burk, if valid, would suggest a latent period sufficiently short for the Canadian study to have demonstrated significant differences in cancer mortality between municipalities supplied with fluoridated water and those with nonfluoridated water.

New Zealand

In New Zealand, fluoridation of municipal water supplies was introduced in 1954, and by 1975 approximately 54% of the country's population were receiving fluoridated water. In 1980 Goodall & Foster (*12*), from the Cancer Registry of New Zealand, identified two population groups, one served at least since 1967 by fluoridated and the other by nonfluoridated water supplies.

Since over 90% of all cancer deaths in New Zealand occur in people aged 45 years and over, these age groups were used for the study. It was found that the cancer death rate for males was 629.5 per 100 000 in the areas which later became fluoridated; this was 11% higher than the rate of 567.7 per 100 000 in the nonfluoridated areas. For females, in 1961, the cancer death rate was 3% higher in the nonfluoridated areas (501.4 per 100 000) than in the fluoridated areas (484.7 per 100 000).

In 1976, after 9–11 years of fluoridation, the cancer death rates for males were 691.1 per 100 000 in the fluoridated areas and 733.5 per 100 000 (6% higher) in the nonfluoridated areas. Thus, for males, the cancer death rate increased more sharply (29%) in the nonfluoridated areas than in the fluoridated areas (10%). In females, the cancer death rates did not show the large increases that were characteristic of males. In nonfluoridated areas, the cancer death rate per 100 000 increased by 2% between 1971 and 1976, but decreased by 5% in fluoridated areas. By 1976, the female cancer death rate was 463.2 per 100 000 in fluoridated areas and 511.9 per 100 000 (11% higher) in the nonfluoridated areas.

The authors concluded that there was no support for the assertion that fluoridation of public water supplies resulted in any increase in cancer mortality. On the contrary, there was some evidence that the rate of increase in cancer mortality over the 15-year period, 1961–76, had been greater in the nonfluoridated areas.

The United Kingdom

Kinlen, in 1975, from the Radcliffe Infirmary in Oxford was the first to use registration data to compare various cancers in areas of England with a high natural fluoride level in water with similar data for areas with low fluoride levels (*16*). For each local authority district in which the mean fluoride level was 1 mg/litre or more, a nearby district was selected in which the water fluoride level was 0.2 mg/litre or less. Urban areas were matched with urban and rural districts with rural.

For each area, cancer morbidity was tabulated by sex and age group for cancers in the following sites: oesophagus, stomach, colon, rectum, breast and bone, related to the years 1961, 1963, 1965 and 1967 only. The data for thyroid, kidney and bladder refer to a longer period (1961–68). The age groupings used were as follows: 0–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and $\geqslant 85$ years. Data for index and control areas were aggregated by sex and age group into four categories according to the fluoride level in the water, and no tendency was found for the number of cancer cases of any organ to be greater in the high-fluoride areas than in the control areas with little or virtually no fluoride in the water.

Similarly, cancer morbidity was also examined in the three areas of England and Wales in which fluoridation schemes had been introduced prior to or during the period to which the cancer incidence data related. However, in the absence of data on the induction periods for the cancers in question, the absence of a tendency for the number of cancer cases to be greater in such areas may be less conclusive than for areas with naturally high fluoride levels. The same may apply to studies of crude incidence data for cancers of the thyroid, kidney and bladder in fluoridated areas in Puerto Rico, New York State, and Connecticut in the USA, the Netherlands, and New Zealand, listed by Kinlen (*16*).

In Birmingham, England, the water supply was fluoridated in October 1964, and it has been claimed by Burk (in letters to officials), that this resulted in an increase in crude cancer mortality (*6*), compared with Manchester where there was no fluoridation. A comparison of data for seven cities, including Birmingham, was therefore undertaken in 1981 by Cook-Mozaffari et al. (*5*) from the Cancer Epidemiology unit in Oxford University. The authors found an increase in age-standardized death rates, for both sexes combined, for all malignant neoplasms in

Birmingham between 1959–63 and 1969–73, amounting to 6.4%. This was almost the same value as seen for the average of the other 6 cities (6.5%) and was centrally placed within the range of values observed, from 2.7% in Sheffield to 9.5% in Liverpool. For 5 of the cities, the increase in cancer death rate over this period was greater than that observed in England and Wales as a whole (5.2%).

Between 1969–73 and 1974–78, the cancer death rate in Birmingham increased by 1.0%, while the other 6 cities experienced an average decrease of 0.9%, and only Sheffield showed an increase (3.4%) greater than that observed in Birmingham. For England and Wales as a whole, the increase was 1.7%. On analysis, it appeared that the differences between Birmingham and the other 6 cities between 1969–73 and 1974–78 were due to changes in cancer death rates for men, while for women the increase was less than the average for the other cities. For neither sex was the observed increase between 1969–73 and 1974–78 statistically significant. For no one type of cancer was there an increase in Birmingham, over one or both periods and for both sexes, that was more extreme than the changes observed in the other 6 cities. It was concluded that there was no reason to suppose that any single factor, such as the fluoridation of water supplies, had affected the cancer death rates in Birmingham since 1964.

In a second study, by Cook-Mozaffari & Doll (*6*), an analysis of the data from which Burk had made his postulate of an increase of cancer mortality in Birmingham was attempted. By recalculation it was shown that changes in the administrative city limits had influenced Burk's calculations and that, even after his corrections, the annual crude cancer death rates for the cities in question showed nothing exceptional for Birmingham. Furthermore, it appeared that there were considerable variations between individual years, so that, since the rate for Birmingham for 1964 was below the rates for either 1963 or 1965, the inclusion of 1964 in the regression analysis for both the pre-fluoridation and the post-fluoridation periods served to heighten the impression of an abrupt change in rates commencing in 1964. The same resulted from the exclusion of the years 1953 and 1954, and the years 1971–77 which had been included in the original analysis of data for Birmingham and Manchester.

Cook-Mozaffari & Doll also commented on other communities within the United Kingdom where fluoridation of water supplies had continued for long enough for any effect that might have been produced to become apparent. An earlier examination of cancer mortality data by Kinlen et al. (*19*), reported in a letter to *Lancet* in 1980, compared cancer mortality trends in the Birmingham and Solihull areas with those in the rest of the West Midlands conurbation for the periods 1959–63 and 1969–73 and found an increase of 6.1% for Birmingham and Solihull, compared with an increase of 9.0% for the rest of the West Midlands. Supplementary comparison of the data for 1959–63 with those for 1974–78 showed increases of 6.3% and 8.3% respectively.

From Anglesey, fluoridated in the mid-1950s, Wynne Griffith had informed Cook-Mozaffari & Doll (*6*) of an increase in cancer mortality between 1949–53 and 1959–63 of 11.1% and a decrease between 1959–63 and 1969–73 of 8.0%. If cancers of the lung and bronchus were removed from the total, the increase for other malignant neoplasms between 1949–53 and 1959–63 was only 1.8%, while the decrease between 1959–63 and 1969–73 was 16.7%.

The USA

Kuzma et al. (*21*), from the Department of Environmental Health in the University of Cincinnati, in 1977 found that 42 out of the 88 counties of Ohio were served by ground water and the remaining 46 by surface water, according to the 1963 inventory of municipal water facilities. They compared the average cancer mortality rates in the surface-water and ground-water counties during the 1956–69 period, using analysis of covariance, and found that the rates for stomach and bladder cancers and for all malignant neoplasms among white males were higher in counties served by surface-water supplies than in counties served by ground-water supplies. The mortality rates for stomach neoplasms among white females were also higher in the surface-water counties. In contradistinction, mortality from lung cancer in white males and from breast cancer in females were not associated with a difference in ground- and surface-water sources after adjustment, while mortality rates for all other cancers in the respective sex showed essentially the same features as the analyses of all cancers mentioned above. These authors found that the differences in mortality rates were not attributable to factors known to be associated with cancer death rates, including urbanization, median income, population size, and occupation in the manufacturing industries, agriculture, forestry or fisheries.

In a study of 57 cities in the United States with populations of 250 000 or more in 1970, Erickson, from the Centers for Disease Control in Atlanta, Georgia, in 1978 found 24 with water supplies that had been fluoridated since before 1960, which meant that the fluoride concentration had been maintained at an optimum level, or the naturally occurring level of fluoride was $\geqslant 0.7$ mg/l (*10*). In the years 1969–71, there were 570 671 deaths among 15 972 817 blacks and whites in the 24 cities with fluoridated water, compared with 351 053 deaths among 11 106 746 people living in the remaining cities. Thus,

the crude death rates for all causes were 1190.9 (for the fluoridated cities) and 1053.6 (nonfluoridated cities) per 100 000 person-years. Adjustments for sex, age and race reduced the differences for some causes and removed them for others. Further correction, using analyses of covariance for urban characteristics that influence mortality, gave adjusted death rates in the cities with fluoridated and nonfluoridated water, respectively, of 1123.9 and 1137.1 (from all causes) and 195.3 and 196.9 (from malignant neoplasms). There was, therefore, no evidence for a harmful effect from fluoridation within the period of observation.

Rogot et al. (*26*), from the National Institutes of Health (Epidemiology Branch for Heart Diseases), in 1978 found that out of 484 urban areas of the United States that had populations of over 25 000 in 1950, 227 had originally been receiving water with a low fluoride content, then became fluoridated, and maintained complete and continuous fluoridation until 1970. Of the remaining cities that never fluoridated, 187 had a water supply with an average fluoride content of less than 0.7 mg/l and 26 had fluoride levels ranging from 0.7 to 2.7 mg/l.

Average mortality ratios were obtained for groups of cities by adding up the mortality ratios for each city and dividing by the number of cities in the group, equal weight being given to all the cities. In preliminary analyses, average mortality ratios weighted by city size were also used. For the analyses, there were two groups: the 227 cities that had become fluoridated in the period 1945–69, and the 187 cities with a low natural fluoride level that had not fluoridated by 1970.

Changes in mortality rates over the 20-year period showed no consistent relation between fluoridation and the observed changes in mortality, whether from all causes of death or from heart disease or cancer. The findings were essentially the same when absolute changes in mortality were studied. The observed changes in mortality ratios for the fluoridated and nonfluoridated cities, according to population size or region of the country, also showed no consistent relationships, whether deaths from all causes or from heart disease or from cancers only were considered.

SUMMARY AND CONCLUSIONS

Since 1945, artificial fluoridation of water supplies has been used in many countries to prevent dental caries in areas where the natural fluoride content in water is low. According to numerous authors this preventive effort has been very successful.

An allegation that artificial water fluoridation may be associated with an increased risk of cancer comes from a single source, which has been published in various versions and reported to committees serving the United States House of Representatives. These publications are by the biochemists, Dr John A. Yiamouyiannis and Dr Dean Burk, and they purport to demonstrate, based on a comparison of cancer mortality rates for communities residing in fluoridated and nonfluoridated cities in various parts of the USA, an association between fluoridation of water supplies and increased mortality from cancers of all sites.

It should be emphasized that even if such a positive association could be demonstrated, it would not necessarily indicate a causal relationship because of the many interrelating factors. The original documentation utilizing crude rates, i.e., the number of deaths divided by population numbers, is not valid evidence for even a statistical association, since it is a fundamental fact in statistics that the various sites and types of cancer may vary in their frequency with age, sex, and certain socioeconomic and ethnic factors. In consequence, the evidence presented by Yiamouyiannis & Burk does not meet the usual requirements for treatment of the data. Also the age groups they used in some of their analyses were very broad, combining in one figure the affected men and women, whites and non-whites, and the tests that were used to see whether race and sex were relevant factors did not overcome this defect.

Meanwhile, several scientists experienced in this field of investigation both in the USA and in the United Kingdom have re-examined the controversial data of Yiamouyiannis & Burk and, using various valid statistical methods, failed to demonstrate any reality in the claim that fluoridation was associated with a cancer risk. Equally, several studies using different data in a number of countries have also given negative results for such an association. Moreover, there is no evidence of any mutagenic effect of fluorides on bacteria or of a carcinogenic effect on experimental animals; nor have teratogenic or genetic effects on man been demonstrated with certainty.

This misleading and refuted suggestion of an association between artificial fluoridation and cancer, which, even if true, would not have proved a causal relationship, has been responsible for a considerable waste of effort and resources that are sorely needed for research and prevention in other fields. It has also served to misrepresent to the press, the public and the politicians in many countries the facts about a very effective and simple way to prevent dental caries in populations.

Finally, the example of lung cancer may be cited. In 1950, five first-rate scientific studies demonstrated a direct association between cigarette smoking and cancer of the lung. Both in this case and in fluoridation, the use of statistics for unjustified criticism has caused long delays in deriving the public health benefits from simple and safe preventive methods.

RÉSUMÉ

PRETENDUE RELATION ENTRE LA FLUORATION DES APPROVISIONNEMENTS EN EAU ET LE CANCER

Depuis 1945, la fluoration artificielle des approvisionnements en eau a été pratiquée dans beaucoup de pays pour prévenir les caries dentaires dans des zones où la teneur naturelle en fluor est peu élevée. De nombreux auteurs estiment que cette action préventive a été très efficace.

L'opinion selon laquelle la fluoration artificielle de l'eau peut entraîner un risque accru de cancer est venue d'une seule source, qui a publié différentes versions de l'argumentation contre la fluoration et qui a fait rapport à des comités attachés à la Chambre des Représentants des Etats-Unis. Les auteurs en sont deux biochimistes, le Dr John A. Yiamouyiannis et Dr Dean Burk. Sur la base d'une comparaison des taux de mortalité par cancer parmi les habitants de villes qui étaient alimentées en eaux fluorées et d'autres qui ne l'étaient pas dans diverses régions des Etats-Unis, ils pensent avoir prouvé l'existence d'une relation entre la fluoration des approvisionnements en eau et l'augmentation de la mortalité par cancers de toutes localisations.

Il convient de souligner que même si une relation positive peut être mise en évidence, elle n'implique pas nécessairement un lien de causalité en raison de l'existence de nombreux facteurs de confusion. Ainsi qu'il est généralement reconnu, les cancers des différentes localisations, pour la plupart, augmentent en fréquence avec l'âge. De même, le sexe et certains facteurs socio-économiques ou ethniques influent sur l'incidence des cancers des différentes localisations, de sorte qu'il faut les prendre en compte lorsqu'on compare les cas de cancer dans différentes populations.

Toutefois, lorsque Yiamouyiannis et Burk ont tenté initialement de faire la preuve d'une plus forte incidence des cancers dans les villes où la fluoration artificielle est pratiquée, ils se sont appuyés sur les taux bruts, c'est-à-dire sur les taux obtenus en divisant le nombre des décès par le chiffre de population. Après avoir eu connaissance des critiques, ils ont fait usage de très grands groupes d'âge dans leurs ajustements pour les différences de distribution en fonction de l'âge entre les populations comparées, en combinant en un seul et même chiffre hommes et femmes affectés, Blancs ou non-Blancs. Les tests pratiqués pour déterminer si la race et le sexe étaient des facteurs déterminants n'ont pas éliminé ce défaut.

A l'inverse, différentes équipes de scientifiques ont constaté au cours de la période où les approvisionnements en eau avaient été traités qu'il y avait eu dans les villes en question une augmentation de la poulation non blanche et de la population de Blancs âgés, soit deux groupes à mortalité par cancer relativement élevée, de sorte que les taux ajustés étaient à peu près les mêmes dans les villes où la fluoration n'était pas pratiquée. Ces observations ont été confirmées par d'autres faites aux Etats-Unis, au Royaume-Uni, au Canada, en Nouvelle-Zélande, en Australie et en Autriche.

L'article souligne en conclusion que cette question futile a été l'occasion d'un gaspillage considérable de travail et d'argent qui seraient si nécessaires pour d'autres domaines de la recherche.

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